MEDICINAL CANNABIS ACCESS IN ACCORDANCE WITH THE PROVISIONS OF SECTION 22A and 22C (1)(b) OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 of 1965)

The Medical Innovation Bill, 2014 (PMB1 2014)

On 18 February 2014, Government Gazette Vol 584, Gazette Notice 37349, a private members Bill by Mario Oriani-Ambrosini (MP), the so-called *Medical Innovation Bill* was published that provides for:

- innovation in medical treatment
- legalising the use of cannabinoids for medical purposes
- legalising commercial and industrial use of cannabis.

The purpose of the Bill is to:

- allow innovation in medical treatment, where medical practitioners depart from traditional treatment regimens when existing evidence-based treatments are no longer supportive of patients
- prevent reckless, illogical and unreasonable departure from standard practice
- legalise and regulate the use of cannabis for medicinal purposes
- legalise cannabis for commercial and industrial use

The Bill states that treatment (without defining the specific treatment) be provided in pre-identified health facilities and that the medical practitioner considers the risks and likely success-rate when compared to other treatments and that the necessary informed consent be obtained from the patient.
The Bill then specifically addresses Cannabinoids (dagga) declaring that no person will be liable or guilty of any offence for growing, processing, distributing, using, prescribing, advertising, dealing with or promoting cannabis for purposes of **treatment** and **commercial and industrial** use or products as identified by the Minister of Trade and industry (DTI).

Of note, a similar Bill was tabled in the UK Parliament on 8th June 2015, i.e. the Medical Innovation Bill (Saachi Bill), to encourage responsible innovation in medical treatment and to allow medical doctors to depart from existing and acceptable medical treatments for a condition. The UK Bill provides for the same

arguments as the Medical Innovation Bill in SA except that the explicit use of Cannabis is not addressed. The UK Medical Innovation Bill has not progressed in the UK Parliament in its current format.

The Legal Status of Cannabis in South Africa

Cannabis is classified as a narcotic drug under Schedules I and IV of the 1961 United Nations (UN) Single Convention on Narcotic Drugs, making it subject to special restrictions. South Africa is a signatory to this UN convention and is required to ensure that drug-related activities such as cultivation, production, trade, possession and use are prohibited by law.[1] Article 2 of the 1961 Single Convention provides for the following, in reference to Schedule IV drugs:

"A Party shall, if in its opinion the prevailing conditions in its country render it the most appropriate means of protecting the public health and welfare, prohibit the production, manufacture, export and import of, trade in, possession or use of any such drug except for amounts which may be necessary for medical and scientific research only, including clinical trials therewith to be conducted under or subject to the direct supervision and control of the Party".

This provision, whilst allowing member countries to determine the most appropriate measures required to protect public health, provides for the **limitation of cannabis to medical and scientific research purposes only.** Whilst cannabinoids have been shown to be useful in a few medical indications, research in this area is ongoing and its use for this purpose is already enabled in current South African legal provisions. The chemical content and make up of cannabis is rather unique; it contains over 400 compounds, including over 60 cannabinoids which are unique to the plant. Moreover, over the past 20 years sophisticated cultivation methods (such as hydroponic farming) and plant-breeding techniques have greatly increased the potency of cannabis products. This process of selective growing has substantially increased THC content over the years, from 1–3 % in the 1970s to 6–13 % and higher today. Sinsemilla and Netherwood varieties of cannabis may have a THC content of up to 20 % higher. Thus, current users of cannabis may have very different experiences to those of the past. This is an important fact since the effects of THC are dose-related and most of the research on cannabis was carried out in the 1970s using doses which were much lower (10-fold) than are found in preparations available today.

[1] Single Convention on Narcotic Drugs, 1961 as amended by the 1972 Protocol. United Nations.

As per the current legal position in the South Africa, the possession and supply of cannabis is illegal.
In South Africa, cannabis is controlled in line with the 1961 Single Convention and is listed in various pieces of legislation including:

- the Drugs and Drugs Trafficking Act, 140 of 1992, sections 4(b) and section 5(b), read with Part 3 of the Schedule 2 of
- the Medicines and Related Substances Act, 101 of 1965; section 22A read with Schedule 7
- the Criminal Procedure Act 51 of 1977; section 40(1)(h)

In terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), Cannabis is listed as a controlled substance in Schedule 7 with Section 22A (9)(a)(i) of the Act providing that no person may acquire, use, possess, manufacture or supply cannabis as the whole plant or any portion or product thereof, and includes synthetic cannabinoids (see below). This section of the Act also makes provision for the Director-General to issue a permit authorising a medical practitioner, analyst, researcher or veterinarian to use cannabis, on the prescribed conditions, for the treatment or prevention of a medical condition in a particular patient, or for the purposes of education, analysis or research.

In addition, the Medicines Act, allows cannabis to be used as hemp fibre or in a processed product provided that the hemp fibre does not contain more than 0,1 percent THC or in the case of a processed product, not more than 0,001 percent THC and is in a form that does not contain cannabis seeds and is not suitable for ingestion, smoking or inhaling purposes.

Based on the uncontroverted evidence of the harmful effects of cannabis, the Department of Health supports the position taken by government to continue to regulate the use of cannabis. The prohibition seeks to prevent harmful effects of cannabis which has the potential to produce psychological dependence.

The current inscription for cannabis in the Schedules to the Medicines Act reads as follows:

SCHEDULE 7

Preamble:

"All preparations or mixture of such substances containing or purporting to contain substances referred to in this Schedule include the following (unless expressly excluded or unless listed in another Schedule):

(i) *the isomers of such substances, where the existence of such isomers is possible within the chemical designation;*

(ii) *the esters and ethers of such substances and of the isomers referred to in (i), as well as the isomers of such esters and ethers, where the existence of isomers of such esters, or ethers is possible;*

(iii) *the salts of such substances and of the isomers referred to in (i), as well as the salts of the esters, ethers and isomers referred to in (ii), where the existence of such salts is possible;*

(iv) *the isomers of any of the salts referred to in (iii), where the existence of such isomers is possible;*

(v) *all preparations and mixtures of any of the above.*

(vi) *all homologues of listed substances unless listed in another Schedule*

Schedule 7 inscription for Cannabis:

Cannabis (dagga), the whole plant or any portion or product thereof, except:

a. *when separately specified in the Schedules; (S6) or*
b. *processed hemp fibre containing 0.1 percent or less of tetrahydrocannabinol and products manufactured from such fibre, provided that the product does not contain whole cannabis seeds and is in a form not suitable for ingestion, smoking or inhaling purposes; or*
c. *processed product made from cannabis seeds containing not more than 10 milligram per kilogram (0,001 percent) of tetrahydrocannabinol and does not contain whole cannabis seeds."*

["Processed" means treated by mechanical, chemical or other artificial means but does not include- (a) harvesting; or (b) the natural process of decay"].

Additionally, Schedule 7 also contains the following inscription relating to synthetic cannabinoids:

"Synthetic cannabis substances (synthetic cannabinoids) included but not limited to:

- *cannabicyclohexanol;*
- *JWH-018; JWH-073; JWH-200; CP-47497; CP 47497-C6; CP 47497-C7; CP 47497-C8; CP 47497-C9; HU-210"*

In its 1994 annual report, the International Narcotic Control Board (INCB) recommended that member countries establish licensing and registration regulations, define the control systems for hemp cultivation

and also properly define which cannabis varieties are authorised for cultivation. Further, it is worth noting that the INCB continues to oppose cannabis reform at the international level which refers to efforts to ease restrictions on cannabis use under international treaties.

Following numerous studies conducted on behavioural effects of Cannabis in adolescence, the known dependence syndrome and its psychosis effects; prevention of cannabis abuse remains a necessity and a public health priority.

In terms of the Medicines and Related Substances Act, 1965, South Africans can be authorized through their health care practitioners to use cannabis for **medicinal** purposes. Therefore, a prescription is required to be issued to a patient. The Medicines Act does not allow for recreational use of the substance. In addition, since cannabis is a controlled substance and listed in Schedule 7, the Director General: Health (DG) is required to issue a permit to a patient to obtain the product and have it in his/her possession. Patients who are in possession of both a prescription and permit from the DG can source a cannabis product in the following ways:

- Pharmaceutical cannabis products registered by the MCC
- Unregulated illegal herbal cannabis, which may be grown or bought from the black market and generally has unknown concentrations of cannabinoids and potentially harmful contaminants.
- Controlled and standardised herbal cannabis products obtained from licensed producers, which have standardised levels of cannabinoids and tested to be free of harmful contaminants.

The current legislation does not yet provide for option 3 however the Medicines and Related Substances Amendment Act, 2015 (Act 14 of 2015) that awaits proclamation by the State President provides for the said licensing of API / Schedule substance manufacturers.

In an attempt to support access to locally manufactured medicinal cannabis products for use in exceptional circumstances, Regulation and Guidelines are under development by the MCC in support of the provisions of Section 22A (9) of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) including the issuing of licenses to growers who intend to supply a standardised, quality controlled substance to patients.

The Department of Health has committed to this change as no patient should have to choose between breaking the law and suffering. The intention is to allow an amendment to current legislation in order to allow people in exceptional circumstances to safely access medicinal cannabis products.

The following recommendations and key issues are being addressed:

- Cultivation, manufacture and supply of standardised, high quality medicinal cannabis products
    - A key step to enabling access to medicinal cannabis will be to establish cultivation and manufacturing industries to support an ongoing and reliable supply of quality medicinal cannabis for patients
    - The Department of Health, Director General will regulate growers of medicinal cannabis by issuing a permit to allow for the controlled cultivation of cannabis for the purpose of medicinal cannabis.
- Patient eligibility
    - Eligibility for access to medicinal cannabis products will, as an initial phase, take the following indications and conditions into consideration:
        - Severe muscle spasms or severe pain in patients with multiple sclerosis
        - Severe pain, nausea, vomiting or wasting arising from cancer, HIV/AIDS (including of the treatment thereof)
        - Severe seizures resulting from epileptic conditions where other treatment options have failed or have intolerable side effects
        - Severe chronic pain with the approval of at least two specialists
- Appropriate clinical oversight involving specialists, general practitioners, nurses and pharmacists
- The need for ongoing research and clinical trials.
    - The Department of Agriculture will be required to pronounce on the outcome of the cultivation trials at the 4 research facilities which are jointly overseen by the Department of Health and Department of Agriculture
    - To strengthen the current evidence base, the Medical Research Council and other academic research centres will be supported to conduct ongoing research on the clinical use of medicinal cannabis.

The Department of Health, in consultation with the Medicines Control Council will establish a dedicated Medicinal Cannabis Unit within the Department of Health to oversee cultivation, manufacturing,

dispensing and clinical aspects of the framework as well as to encourage new research, develop clinical guidance in consultation with the medical profession, and provide advice about eligibility of patient groups.

Ongoing work under the guidance of the Medicines Control Council includes review of clinical use, clinical and scientific research, and pharmacological aspects.

In order for South Africa to honour its obligations under the United Nations treaties (UNODC is continuously monitoring and conducting research on global illicit drug markets in order to gain a more comprehensive understanding of their dynamics) and its SADC treaties (SADC Drug Protocol, 1996), the Department of Health is working closely with the International Narcotic Control Board, the United Nations and SADC to ensure that patients requiring medicinal cannabis can access medicinal cannabis safely and legally.

Cannabis remains an integral part of the illicit drug trafficking trade driven through organized crime and legalising cannabis would reverse the gains made in the war against organised crime resulting from illicit drug trafficking. Furthermore, the current high levels of abuse and misuse amongst adolescents and young adults remains a major concern. A discussion paper published in the SAMJ recently reflects a discussion of the Central Drug Authority (CDA) within the Department of Social Development regarding the decriminalization of cannabis for non-medicinal use within the South African context. Of importance, this discussion reflects the difference between legalisation and decriminalization.

Legalisation of cannabis implies that no person can be arrested or convicted for possession or any related offense. With decriminalization, this remains a criminal act but no longer subject to prosecution provided that the person has in his/her possession small quantities (the maximum amount to be stipulated in legislation) for personal use. The person will not be prosecuted and will not receive a criminal record or jail sentence. On the other hand, the possession of large quantities of cannabis or the selling thereof would still be subjected to certain penalties.

The Department of Health and the Medicines Control Council is in the process of introducing guidelines and procedures to enable a more accessible regulatory framework and to allow for easier access to medicinal cannabis products for medical purposes.

RECOMMENDATIONS

Regarding the Medical Innovation Bill, 2014, the Department of Health is of the view that:

- Innovation in medical treatment is already addressed by the Medicines and Related Substances Act, 1965 and specifically Section 21 of the Act, which allows for the use of an investigational product or unregistered medicine:
    - For clinical research purposes or by a medical practitioner (therefore enabling departing from standard evidence-based treatment regimens which no longer provide benefit for a patient through appropriate controls, whilst at the same time preventing reckless, illogical and unreasonable practices)
    - For a specific patient, for a specified period and under controlled conditions

- It is the view of the Department of Health that the current legislative framework of the Medicines and Related Substances Act, 1965 already provides for the legalisation of the use of cannabinoids for medicinal purposes as well as for commercial and industrial hemp production. In addition the Medicines and Related Substances Amendment Act, 2015 (Act 14 of 2015) [to be proclaimed by the President during 2016} allows for the licensing of manufacturers of Scheduled substances. The Department of Health and Medicines Control Council (MCC) will therefore be able to license producers and growers of cannabis for medicinal purposes, attach conditions to their license, and comply with the directives of the International Narcotic Control Board (INCB) to establish licensing and registration procedures.

- The key elements of the framework being implemented by the Medicines Control Council and the Department of Health includes the following:
    - Licensing of growers to enable controlled cultivation for medical, scientific and research purposes.
    - Availability of a standardised, quality-assured product for medical use indications.
    - Clinical decision-making support for approval of medical use in terms of Section 22A(9)(ii) and Section 21 of the Medicines Act.
    - Review and approval of clinical trials and related scientific research in terms of Section 21 of the Medicines Act.

Annexure I

Patterns of Cannabis Use Globally and in South Africa

Background

In many countries, cannabis use increased during the 1990s and early 2000s, but is now generally stabilizing. Rates of use, however, are not low and it is estimated that between 2.8% and 4.5% of the world population aged 15-64 used cannabis at least once during the past year in 2009.[1]

The annual prevalence of cannabis use in North America is approximately 10.7% of the population aged 15-64, and use among the youth has risen over the past four years. Africa has the third highest cannabis prevalence rate in the world, after the Oceania region and North America, with estimates ranging from 3.8% to 10.4% of the population.

In South Africa, cannabis remains the most common illicit drug used, especially among youth attending specialist treatment centres. Cannabis is the most common primary substances of abuse for patients younger than 20 years, with up to 78% of patients being Black.[1] Additionally, treatment admissions with cannabis as the primary drug of abuse has increased significantly in almost all provinces and regions in the country. Cannabis is the illicit drug most likely to be consumed by high-school students and is commonly used by young rave club attendees. Although many young people do not perceive cannabis to be a problem, the South African Community Epidemiology Network on Drug Use (SACENDU) adolescent treatment demand, trauma, and arrestee data clearly reflect the burden that cannabis use has to the health, social welfare, and criminal justice systems in South Africa.[16]

Peltzer and Ramlagan recently reviewed cannabis use trends (over a period of 12 years) in the South African population, by sourcing data from surveys, specialised alcohol and drug treatment centres, cannabis-related trauma unit admissions, and arrestee studies.[2] They concluded that cannabis was the most common illicit substance used, with current self-reported cannabis use of 5 - 10% among adolescents and 2% among adults. Furthermore, it was higher among men than women, higher in urban than rural areas, higher in the urban provinces of Western Cape and Gauteng than the other provinces, and higher among coloureds and whites than other racial groups.

Heavy cannabis use is generally defined as daily or near daily use and this pattern of use over years places users at greatest risk of adverse health and psychological consequences. Daily cannabis users are more likely to be male, to be less well educated, to use alcohol and tobacco regularly, and to use amphetamines, hallucinogens, psychostimulants, sedatives, and opioids.

Combination of Cannabis with other Drugs

An obvious confounding factor in cannabis research is the concomitant use of other recreational drugs, especially alcohol and tobacco.[3] Such complications demonstrate the need for studies on

[1] SACENDU Report. Phase 34. February 2014.
[2] Peltzer K, Ramlagan S. (2007). Cannabis use trends in South Africa. South African Journal of Psychiatry. 13(4): 126-131.
[3] Zhang Z, Morgenstern H, et al. (1999). Marijuana use and increased risk of squamous cell carcinoma of the head and neck. Cancer Epidemiology, Biomarkers and Prevention 8 (12): 1071–8.

cannabis that have stronger controls, and investigations into effects of cannabis that may also be caused by other drugs. The Australian National Household Survey of 2001[4] showed that cannabis is rarely used without other drugs: 95% of cannabis users also drank alcohol; 26% took amphetamines; 19% took ecstasy and only 2.7% reported not having used any other drug with cannabis. Evidence also suggests that alcohol causes THC to be absorbed more rapidly into the blood plasma of the user.[5] Of interest, data from the Australian National Survey of Mental Health and Wellbeing found that three-quarters of recent cannabis users reported using alcohol when cannabis was not available.[6]

In South Africa, cannabis is often mixed with other substances including methaqualone[7] (Mandrax), heroin, cocaine and the antiretroviral (ARV) agent efavirenz[8]. In addition, mixtures having street names such as 'Nyaope', 'Sugars', 'Whoonga', etc., contain varying amounts of cheap heroin and cocaine, and are usually smoked with cannabis. These street concoctions often also contain other substances such as rat poison, cleaning detergents, efavirenz, methamphetamine and other illicit drugs. Street use of the ARV efavirenz may exploit its well-known central nervous system effects which may enhance the effects of cannabis, heroin, methamphetamine, and other illicit drugs. Recent data suggest that an increasing number of young people are presenting for assistance at treatment centres relating to abuse of 'Nyaope', 'Sugars' and 'Whoonga'. A total of 1537 patients were treated across the seven treatment centres during the second half of 2008 alone.[9]

Cannabis smoked with methaqualone is known by the street name 'white pipe' in South Africa and is associated with a number of negative health outcomes, including dependence.[10] Methaqualone users, in particular, have a high risk of becoming physically and psychologically dependent on the drug.[11] In addition, the frequent and prolonged use of cannabis in this population of users may lead to psychological dependence, tolerance, and withdrawal symptoms on cessation of use.[12] The prolonged use of cannabis and white pipes may also lead to respiratory problems, including pre-cancerous changes in lung tissue, and significantly more abnormalities in the pulmonary bronchi, respiratory illnesses, and symptoms of chronic bronchitis than occur among non-users.[13]

Discussion

The available data on cannabis misuse in South Africa presented here clearly highlights its adverse sequelae, particularly in adolescents. These effects are wide ranging and its use is linked to addiction, cognitive impairment, motor skills deficiency, respiratory, cardiovascular and mental health problems. Additionally, recent emerging evidence showing an increased risk of adverse developmental outcomes

[4] National Drug Strategy Household Survey (2001). Australian Institute of Health and Welfare.
[5] Lukas SE, Orozco S. (2001). Ethanol increases plasma Δ9-tetrahydrocannabinol (THC) levels and subjective effects after marihuana smoking in human volunteers. Drug and Alcohol Dependence 64 (2): 143–9.
[6] Hall L, Degenhardt W. (2001). The relationship between tobacco use, substance-use disorders and mental health: results from the National Survey of Mental Health and Well-being. Nicotine & Tobacco Research 3 (3): 225–34.
[7] de Miranda S. Drugs and Drug Abuse in Southern Africa. Pretoria: JL Van Schaik. 1987: 32-35.
[8] Larkin F, van Wyk B, et al. (2010). Of Remedies and Poisons: Recreational Use of Antiretroviral Drugs in the Social Imagination of South African Carers. African Sociological Review 14(2): 62-73
[9] SACENDU Research Brief Vol 12(1) 2009.
[10] Bhana A, Parry CDH, et al. (2002). The South African Community Epidemiology Network on Drug Use (SACENDU) Project, Phases 1-8 – Cannabis and Mandrax. SAMJ. 92(7): 542-547.
[11] Faught E. (1986). Methaqualone withdrawal syndrome with photo-paroxysmal responses and high amplitude visual evoked potentials. Neurology. 36: 1127-1129.
[12] Budney AI, Navy PL, Hughes JR. (1999).Marijuana withdrawal among adults seeking treatment for marijuana dependence. Addiction. 94: 1311-1322.
[13] Hall W. (1998). The respiratory risks of cannabis smoking. Addiction. 93: 1461-1463.

in adolescents, is of particular concern. Both local and international experience confirm cannabis as being the most commonly abused drug among adolescent treatment seekers.

Prevention of cannabis abuse therefore remains a necessity and a public health priority. This will contribute to achieving broad health and social benefits through the concurrent implementation of evidence-based prevention and treatment strategies to effectively reduce use, abuse and addiction. Whilst cannabinoids have been shown to be useful in a few medical indications, research in this area is ongoing and its use for this purpose is already enabled in current legal provisions.

Annexure II

Medicinal Cannabis: Current Evidence Base for Efficacy

Introduction

This Annexure[1] provides an understanding of the concept of medicinal cannabis and reviews the research evidence base for the efficacy of cannabis in alleviating the symptoms of particular conditions

What is medicinal cannabis?

The effects of cannabis are affected by the types and amounts of cannabinoids in the product. Products can contain high or low levels of delta-9-tetrahydrocannabinol (THC) or cannabidiol (CBD), in various combinations with the other cannabinoids. Some forms are psychoactive, principally because of their concentration of THC. Cannabis is used for recreational purposes for its euphoriant effect, among other things, but also for medicinal purposes to cure or remedy symptoms of medical conditions.

Cannabis is considered to be used medicinally when it is both:

- taken by a person for the medicinal purpose of attempting to cure or remedy a medical condition, and
- taken in a manner that enables the purported curative or remedial effect to be appropriately supervised and verified by a qualified medical professional.

Products that are extracted from the cannabis plant and used for medicinal purposes are regarded as falling within the meaning of medicinal cannabis.

Cannabis products used medicinally can be categorised according to how their production is regulated:

- Pharmaceutical-grade cannabis products registered by the MCC
- Unregulated illegal herbal cannabis, which may be grown or bought from the black market and generally has unknown concentrations of cannabinoids and potentially harmful contaminants.
- Controlled and standardised herbal cannabis products obtained from licensed producers, which have standardised levels of cannabinoids and tested to be free of harmful contaminants.

Cannabis can also be differentiated by the form in which it is supplied. The categories of product made available for medicinal purposes include:

- the dried flowering tops of the cannabis plant, taken through being smoked, vaporised or infused in tea;
- cannabis resin, collected and compressed from the flowering tops;
- infused cannabis products, such as alcohol-based tinctures, edible oils infused with cannabis and products made from these, and suppositories;

[1] Adapted from the Medicinal Cannabis Report of the Victorian Law Reform Commission (Australia); http://lawreform.vic.gov.au/content/2-use-cannabis-medicinal-purposes

- extracts of cannabis, containing concentrated extracts of cannabinoids, taken orally, topically or by vaporisation;
- raw, undried cannabis leaves, consumed as a food.

Furthermore, THC and CBD are not the only compounds of interest in the cannabis plant. Besides THC, other non-psychoactive and non-addictive cannabinoids may have therapeutic potential and include:

- cannabidiol (CBD) and its acid form (CBDA)
- cannabidivarin (CBDV)
- the acid form of THC (THCA)
- tetrahydrocannabivarin (THCV) and its acid form (THCVA)
- cannabigerol (CBG) and its acid form (CBGA)
- cannabinol (CBN)
- cannabichromene (CBC)

Research on the effects of these cannabinoids remains at an early phase, but these compounds may have possible medical application in the treatment of epilepsy, pain, psychosis, cancer, diabetes, inflammation, anxiety and a host of other conditions.[2]

Research support for efficacy

In determining what the eligibility criteria should be for a framework that allows people to be treated with medicinal cannabis in exceptional circumstances, and when making clinical decisions about a patient's treatment, not all evidence is of equivalent value. A threshold consideration when making these types of decisions regarding medicinal cannabis is the clinical evidence for its efficacy in treating particular conditions and symptoms. The associated risks must also be taken into account.

Partly as a result of the broadly stated, often divergent, claims made regarding medicinal cannabis, it is important that the available evidence is evaluated to determine which claims can be substantiated, and to what degree. The conventional means of doing so is by reference to evidence-based medicine.

Evidence-based medicine and the quality of evidence

Evidence-based medicine is an approach to the practice of medicine that has been described as the 'conscientious, explicit, and judicious use of current best practice in making decisions about the care of individual patients.[3] It aims to improve decision making by medical practitioners about the provision of treatment, by emphasising a systematic approach that critically appraises the available clinical evidence. A cornerstone of evidence-based medicine is the hierarchical system of classifying evidence, often referred to as 'levels of evidence'. Medical practitioners are encouraged to find the highest level of evidence to answer clinical questions, including whether they should prescribe or encourage access to particular forms of medication.

The standard taxonomy of levels of evidence for intervention studies based on international guidelines and starting with the highest quality of evidence, is as follows:

- Level I: evidence obtained from a systematic reviews and meta-analyses of Level II studies;

[2] Izzo AA, Borrelli F, et al, Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009 Oct;30(10):515-27

[3] David L Sackett et al, 'Evidence-Based Medicine: What It Is and What It Isn't' (1996) 312 British Medical Journal 71.

- Level II: evidence obtained from at least one properly designed randomised controlled trial of appropriate size;
- Level III-1: evidence obtained from well-designed pseudo-randomised controlled trials;
- Level III-2: evidence from comparative studies (including systematic reviews of such studies) with concurrent controls being a non-randomised experimental trial, a cohort study, an interrupted time series or matched case-controlled study;
- Level III-3: evidence from a comparative study without concurrent controls, being a historical control study, two or more single arm studies (i.e. case series from two studies), or a well-designed interrupted time series trial without a parallel control group from more than one centre or research group or from case reports; and
- Level IV: evidence obtained from a case series, either post-test or pre-test/post-test outcomes.

The evidence cited in support of the medicinal properties of cannabis ranges across a number of these categories. In the following section, an overview is given of the status of current knowledge about the efficacy of cannabis for conditions regarding which particular claims have been made. The overview emphasises outcomes at the highest level of clinical evidence: systematic reviews and meta-analyses (Level I).

The quality of cannabis research

A substantial body of evidence now exists in relation to the efficacy of certain forms of cannabis for particular medical conditions. There is some evidence to suggest that cannabinoids are effective for the treatment of neuropathic pain, muscle spasticity for patients with MS, and in controlling nausea for cancer patients. However, while this body of evidence exists—and is rapidly expanding—it is of inadequate quality for definitive statements to be made about the therapeutic efficacy of cannabis for many conditions. This causes concern in many quarters of medicine about the legitimacy of prescribing medicinal cannabis. Significant gaps in our scientific understanding remain and that it is important that medicinal cannabis is used to treat identified medical conditions where it has been proven to be safe and effective.

In an editorial in the Journal of the American Medical Association published in June 2015, for instance, D'Souza and Ranganathan argued that for most conditions that have been regarded as appropriate for medicinal cannabis, approval has relied on low-quality scientific evidence, anecdotal reports, individual testimonials, legislative initiatives, and public opinion. … For most of the conditions that qualify for medical marijuana use, the evidence fails to meet [Food and Drug Administration] standards.[4]

It has been argued that there are obstacles to the accumulation of high-quality cannabis research which do not exist for other drugs. For example, conducting research with cannabis or cannabinoids tends to attract much more onerous regulatory complexity than for other drugs. Further, whole-plant forms of cannabis generally do not have a 'sponsor' with a financial interest in funding clinical trials, possibly resulting in fewer or smaller studies.

Evidence for efficacy

The following section discusses particular conditions that have been the subject of recent systematic reviews, meta-analyses and other significant evaluations.

[4] Deepak Cyril D'Souza and Mohini Ranganathan, 'Medical Marijuana: Is the Cart Before the Horse?' (2015) 313 Journal of the American Medical Association 2431.

Multiple sclerosis

The results of a recent meta-analysis by Whiting et al indicate that there is moderate-quality evidence to suggest that cannabinoids may be beneficial for the treatment of spasticity due to [multiple sclerosis].[5] The authors identified 11 placebo-controlled trials meeting the selection criteria, and concluded that studies generally suggested that cannabinoids were associated with improvements in spasticity, but this failed to reach statistical significance in most studies.

Results of trials on the efficacy of cannabis to treat multiple sclerosis are complicated somewhat because there are a number of ways to measure spasticity. Some of these rely on objective measures of spasticity, while others rely on subjective measures, with subjective measures sometimes said to be more informative but complicating the interpretation of trial results. Often research findings depend upon patient self-reports.

Although not conclusive, there is a reasonable level of research support for the effectiveness of cannabis in relieving pain and spasticity for those suffering multiple sclerosis.

Epilepsy

Research to date has delivered results of limited significance. Considerable research energy is being committed to the further study of cannabinoids as a treatment for refractory epilepsy, particularly in juvenile patients.

In 2014, the authors of an article in a medical journal on epilepsy argued that: 'Until data from well-designed clinical trials are available and reliable, and standardised CBD products that are produced using good manufacturing practices are available, caution must be exercised in any consideration of using CBD for the treatment of epilepsy.[6] Also in 2014, the American Society of Neurology expressed the view that the use of oral cannabinoids is of unknown efficacy in epilepsy and that there was not sufficient evidence to prescribe CBD or to recommend self-treatment with medicinal cannabis.[7]

A Cochrane Review[8] published in 2014 on 'Cannabinoids for Epilepsy' reviewed research literature to assess the efficacy and safety of cannabinoids when used as a single therapy or add-on treatment for people with epilepsy. It was very reserved in its findings. It found that 'no reliable conclusions' could yet be drawn regarding the efficacy of cannabinoids as a treatment for epilepsy. It identified only four studies from 1978 to 1990 that met the selection criteria of randomised controlled trials. All used CBD as the treatment agent. It observed that patient numbers in the studies were small (48 patients in total) and that there had been varying reports of reduction in seizure frequency and/ or seizure freedom. The review's authors also expressed the view that, as the studies ran for short periods of time (four weeks to 18 months) the safety of long-term cannabidiol treatment could not be reliably assessed.

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[5] Whiting PF et al, 'Cannabinoids for Medical Use: A Systematic Review and Meta-Analysis' (2015) 313 Journal of the American Medical Association 2456, 2467.

[6] Timothy E Welty, Adrienne Luebke and Barry E Gidal, 'Cannabidiol: Promise and Pitfalls' (2014) 14 Epilepsy Currents 250, 252

[7] Gary W Mathern, Laurie Beninig and Astrid Nehlig, 'Fewer Specialists Support Using Medical Marijuana and CBS in Treating Epilepsy Patients Compared with Other Medical professionals and Patients: Results of Epilepsia's Survey' (2014) 56 Epilepsia 1.

[8] Gloss, David and Barbara Vickrey, 'Cannabinoids for Epilepsy: Review' (2014) 3 Cochrane Database of Systematic Reviews <http://www.thecochranelibrary.com>.

In addition, a systematic review of the efficacy and safety of medical marijuana in treating selected neurological disorders, including epilepsy, was published by the American Academy of Neurology in 2014. It concluded that oral cannabinoids are of unknown efficacy in epilepsy, that the risks and benefits of medical marijuana should be weighed carefully, and that the comparative effectiveness of medical marijuana as against other therapies for epilepsy are unknown.[9]

However, there is some optimism that research currently underway may deliver positive results for treating severe forms of epilepsy.[10] Researchers in the United States presented results at the 2015 Annual Meeting of the American Academy of Neurology from an open-label trial on the treatment of children and young adults suffering from drug-resistant forms of epilepsy with purified CBD (Epidiolex). The trial recruited 213 participants, of whom 123 were included in efficacy calculations. The data showed a median reduction in seizure frequency of 46 per cent by the twelfth week. Patients with Dravet Syndrome had a reduction in seizure frequency of 51 per cent by week 12, while those with Lennox-Gastaut Syndrome experienced a median reduction of 52 per cent. The researchers concluded that CBD showed reductions in seizure frequency across multiple drug-resistant epilepsy syndromes and seizure types and was generally well tolerated in this open-label cohort.

Two Phase III trials using Epidiolex to treat Lennox-Gastaut Syndrome have also commenced, with data expected to become available in early 2016.[11]

Chronic pain

Assessment of the experience of pain is complex. It incorporates complicated overlaps between the physical and the psychological. The concept of exclusively 'physical pain' is no longer accepted in light of our understanding of the neurophysiology and psychology of pain as it has evolved over the past 80 years.

In evaluating the potential contribution of medicinal cannabis to alleviating the experience of patients' pain, it is fundamental to acknowledge that it should only form part of an overall strategy for pain management—it is not the complete answer. Thus it should be integrated, and regulated as necessary, within a broad-based approach to the suffering caused by the experience of pain. It is also important to distinguish between the potential effect of the THC component of cannabis in inducing euphoria and any effect it may have in relieving or alleviating pain.

A systematic review and meta-analysis of cannabis treatment for chronic pain[12], published in 2009, reviewed 18 trials and concluded that cannabis treatment was moderately efficacious for treatment of chronic pain but observed that its beneficial effects may be partially (or completely) offset by potentially serious harms. It concluded that more evidence from larger, well-designed trials was needed to clarify the true balance of benefits to harms.

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[9] B S Koppel et al, 'Systematic Review: Efficacy and Safety of Medical Marijuana in Selected Neurological Disorders: Report of the Guideline Subcommittee of the American Academy of Neurology' (2014) 82 Neurology 1556.

[10] Anup Patel, 'Medical Marijuana in Pediatric Neurological Disorders' (2015) Journal of Child Neurology (published online before print) <jcn.sagepub.com>.

[11] 'GW Pharmaceuticals Initiates Phase 3 Pivotal Study of Epidiolex (CBD) in Lennox-Gastaut Syndrome' (Press Release, 11 June 2015) <http://www.gwpharm.com>.

[12] Eva Martin-Sanchez et al, 'Systematic Review and Meta-Analysis of Cannabis Treatment for Chronic Pain' (2009) 10 Pain Medicine 1353.

A more recent systematic review and meta-analysis, published in June 2015 and including 79 trials with 6,462 participants, also concluded that there is evidence of moderate quality to support the use of cannabinoids for the treatment of chronic pain.[13]

A systematic review of randomised controlled trials examining cannabinoids in the treatment of chronic non-cancer pain published in 2011 reported that 15 of the 18 trials that met the inclusion criteria demonstrated a significant analgesic effect of cannabinoids as compared with placebos and several reported significant improvements in sleep. No serious adverse effects were reported. This led the authors to conclude that there was evidence that cannabinoids were safe and modestly effective in neuropathic pain (nerve pain) with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis. It called for further large studies of longer duration examining specific cannabinoids in homogeneous populations.[14]

Additionally, a Canadian review of the literature in 2014 recommended that smoked cannabis be prescribed by doctors only for severe neuropathic pain syndromes that have not responded to adequate trials for pharmaceutical cannabinoids and other analgesics.[15]

Palliative control of pain

There is some research evidence which supports the capacity of medicinal cannabis (specifically cannabis with a significant THC content) in reducing the severity of pain experienced by persons dying of terminal illnesses, in particular cancer and HIV/AIDS.

There is evidence that cannabis (particularly smoked cannabis) is an effective treatment for pain caused by HIV-associated sensory neuropathy. A systematic review of treatments for the condition published in 2010 located two randomised controlled trials showing superior results for pain relief from cannabis as compared to placebo.[16]

In relation to cancer, there is limited high-quality research literature on the subject. The position of the American Cancer Society remains that it supports the need for more scientific research on cannabinoids for cancer patients, and recognises the need for better and more effective therapies that can overcome the often debilitating side effects of cancer and its treatment.[17]

A 2014 review called for caution: the effectiveness of cannabinoids for the treatment of chronic cancer pain remains unclear, although any benefit is likely to be modest. The available evidence indicates a risk of potentially serious adverse effects, including alterations in perception, motor function, and cognitive function.[18]

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[13] Penny F Whiting et al, 'Cannabinoids for Medical Use: A Systematic Review and Meta-Analysis' (2015) 313 Journal of the American Medical Association 2456.

[14] Mary E Lynch and Fiona Campbell, 'Cannabinoids for Treatment of Chronic Non-Cancer Pain: A Systematic Review of Randomised Trials' (2011) 72 British Journal of Clinical Pharmacology 735.

[15] Meldon Kahan et al, 'Prescribing Smoked Cannabis for Chronic Noncancer Pain: Preliminary Recommendations' (December 2014) 60 Canadian Family Physician 1083.

[16] Tudor J C Phillips et al, 'Pharmacological Treatment of Painful HIV-Associated Sensory Neuropathy: A Systematic Review and Meta-Analysis of Randomised Controlled Trials' (2010) 5(12) PLOS ONE e14433.

[17] American Cancer Society, 'Marijuana and Cancer': <http://www.cancer.org /treatment>.

[18] Farrell M, Buchbinder R and Hall W, 'Should Doctors Prescribe Cannabinoids' (2014) 348 BMJ g2737.

Management of nausea and vomiting

The evidence indicates that medicinal cannabis in a variety of forms can assist in relieving nausea and vomiting and in enhancing appetite.[19] This has the potential to be of particular utility for chemotherapy-induced nausea and vomiting (CINV) and for persons with wasting (cachexia) caused by HIV/AIDS. For instance, a 2008 meta-analysis found that a synthetic cannabinoid was superior to a number of other options for reducing nausea. A variety of studies summarised by Kramer in 2015 have identified efficacy in both respects.[20]

Spinal cord injury

There is some research evidence to suggest that medicinal cannabis can assist with the symptoms associated with spinal cord injury, particularly pain and spasticity. Double-blind, placebo-controlled studies suggest that there may be modest improvements in pain, spasticity, muscle spasms and sleep quality in patients with spinal cord injury. [21,22] Although there is some evidence to support the contention that medicinal cannabis can alleviate some symptoms associated with spinal cord injury, at this stage the research on the issue is at a comparatively early juncture.

Anti-cancer effects

Several cancer cell and tumour models have been used to evaluate the anti-tumour properties of cannabinoids, and increased quantities of endocannabinoid receptors have been detected in various cancer cell lines. While these studies have shown cannabinoids in some cases reduce tumour cell growth, in others they have caused it to increase.[23] The contradictory nature of reports around the efficacy of compounds highlights our lack of detailed understanding of mechanisms of action and potential uses in the clinical setting.

There is no current evidence that cannabinoids are effective at inhibiting tumour growth or treat or cure cancer in humans. In addition, there is no current evidence that cannabis or cannabinoids reduce risk or prevent cancer occurrence or promote good health.

Arthritis

There is a large incidence of patients using cannabis to treat the symptoms of arthritis. As at June 2013, 65 per cent of Canadian patients authorised to receive cannabis reported 'severe arthritis' as their diagnosis.[24] Many forms of arthritis are due to inflammation, and cannabinoids may have potential anti-inflammatory properties, particularly those which act on the CB2 receptor.[25] However, there is scant research support for the efficacy of cannabinoids for pain caused by rheumatoid

[19] Tramèr MR et al, 'Cannabinoids for Control of Chemotherapy Induced Nausea and Vomiting: Quantitative Systematic Review' (2001) 323 BMJ 16.
[20] Joan Kramer, 'Medical Marijuana for Cancer' (2015) 65 CA: A Cancer Journal for Clinicians 109.
[21] Derick T Wade, 'A Preliminary Controlled Study to Determine Whether Whole-Plant Cannabis Extracts Can Improve Intractable Neurogenic Symptoms' (2003) 17 Clinical Rehabilitation 21.
[22] Health Canada, Information for Health Care Professionals: Cannabis and the Cannabinoids (2013) 43 <http://www. hc-sc.gc.ca /dhp-mps /alt_formats /pdf/marihuana /med /infoprof-eng.pdf>.
[23] Belinda J Cridge and Rhonda J Rosengren, 'Critical Appraisal of the Potential Use of Cannabinoids in Cancer Management' (2013) 5 Cancer Management and Research 301, 304.
[24] Mary-Ann Fitzcharles et al, 'The Dilemma of Medical Marijuana Use by Rheumatology Patients' (2014) 66 Arthritis Care and Research 797
[25] Slava Rom and Yuri Persidsky, 'Cannabinoid Receptor 2: Potential Role in Immunomodulation and Neuroinflammation' (2013) 8 Journal of Neuroimmune Pharmacology 608.

arthritis, with a 2014 review concluding that lack of sound evidence for effect, and potential for harm, herbal cannabis cannot be recommended for arthritis pain management at this time. More research in this area is indicated.

Glaucoma

The progression of glaucoma has been shown to be slowed by the lowering of intraocular pressure. Many glaucoma drugs cause side effects which patients find unacceptable. There is some evidence that THC may reduce intraocular pressure, and a possible mechanism has been identified.[26] Other studies have shown promising results using cannabinoids.[27] However, it appears that the effects of cannabis on intraocular pressure are of short duration, by contrast with other therapeutic options, and not sustained over time.

Managing risk with medicinal cannabis

All medicines come with some risk of adverse side effects or toxicity. What is important is whether the medicine's benefits outweigh its risks. A medicine can be very risky—for example, because it is very toxic—and still be justified because it is necessary to treat a serious condition. What is of concern, particularly to medical practitioners, is that the risks of cannabis are inadequately known and so no assessment can be made of its benefit to a patient on balance. In particular, while there is reasonable knowledge of the risks posed by recreational use of cannabis, there are very few studies as yet on the side effects of medicinal cannabis, including non-smokable forms. This is especially so in respect of medium-term and long-term risks for different categories of patients with different vulnerabilities

It is important that any medicinal cannabis framework acknowledges the reality of a diverse range of actual and potential side effects for patients. However, such side effects generally arise from cannabis with a significant THC content and may be less relevant in the context of cannabis that has a high CBD content.

Many potential side effects can be minimised by avoiding uncertain and excessive levels of consumption arising from self-administration and also by minimising the use of smoked forms of cannabis.

Most prescribed medications have side effects for which appropriate warnings are given to patients by their medical practitioners and pharmacists so that the consent that patients (or those responsible for them) provide is properly informed. In addition, a fundamental responsibility of medical practitioners is to review the condition of patients for whom they prescribe in order to identify not only the correct level of medication to address patients' symptoms but also the onset of any side effects, so that these can be addressed. Medicinal cannabis is no different from other medications in this regard, except that for the most part the side effects arising from the use of medicinal cannabis are unlikely to be life-threatening provided that suitable steps to avoid misuse are taken by medical practitioners.

[26] Anna Porcella et al, 'The Human Eye Expresses High Levels of CB1 Cannabinoid Receptor mRNA and Protein' (2001) 12 European Journal of Neuroscience 1123.
[27] I Tomida et al, 'Effect of Sublingual Application of Cannabinoids on Intraocular Pressure: A Pilot Study' (2006) 15 Journal of Glaucoma 349.